REMARKS

The remainder of this Reply appears under the appropriate subheadings for the convenience of the Examiner.

Telephonic Interviews with the Examiner

Applicants' Attorneys, Mary K. Murray and N. Scott Pierce, conducted a telephonic interview with Examiner Afremova on February 17, 2004. In the telephonic interview, Examiner Afremova indicated that she would provide an Interview Summary in the next Office Action. No Interview Summary and no reference to the February 17, 2004 telephonic interview was included in the Office Action. Applicants respectfully request that Examiner Afremova provide an Interview Summary of the February 17, 2004 telephonic interview with the next Office Action.

On June 21, 2004, Applicants' Attorney, Mary K. Murray, spoke to Examiner Afremova regarding the filing of an RCE and accompanying Reply to the Office Action Made Final in July, 2004. Examiner Afremova indicated she would grant an in-person or telephonic interview following the filing of the RCE and Reply.

Applicants thank Examiner Afremova for the telephonic interviews.

Information Disclosure Statements

Applicants hereby bring to the attention of the Examiner the fact that a transmittal of the Sixth Supplemental Information Disclosure Statement, filed March 4, 2003, citing U.S. Patent Application No. 10/251,685, filed September 20, 2002 (Docket No. 2831.2003-001) as a non-published pending application and the PTO Form 1449 associated with the Seventh Supplemental Information Disclosure Statement, filed on August 7, 2003, (reference AS6) were not returned by the Examiner in the Office Action. For the Examiner's convenience, a copy of the Sixth Information Disclosure Statement and date-stamped postcard receipt, filed by Certificate of Mailing on March 4, 2003; and the Information Disclosure Statement, PTO Form 1449 and date-stamped postcard receipt for the Seventh Supplemental Information Disclosure Statement, filed by Certificate of Mailing on August 7, 2003, are enclosed with this Reply.

Applicants respectfully request consideration of the non-published application cited in the Sixth Supplemental Information Disclosure Statement filed March 4, 2003 and the Seventh Supplemental Information Disclosure Statement, filed by Certificate of Mailing on August 7, 2003. Applicants request that the Examiner initial the transmittal form accompanying the Sixth Supplemental Information Disclosure Statement indicating consideration of the non-published Patent Application No.: 10/251,685 and PTO Form 1449 accompanying the Seventh Supplemental Information Disclosure Statement with a subsequent Office Action.

Rejection of Claims 14, 19, 20, 23, 24 and 26 under 35 U.S.C. § 103(a)

Claims 14, 19, 20, 23, 24 and 26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application No. 2002/0168765 A1 by Prockop, D.J., *et al.* (hereinafter "Prockop"), WO 01/34167 by Prockop, D.J., *et al.* (hereinafter "Prockop II") and WO 01/11011 by Furscht, L.T., *et al.* (hereinafter "Furscht") in light of evidence by U.S. Patent No. 5,837,539, issued to Caplan, A.I., *et al.* (hereinafter "Caplan") and Colter, D.C., *et al.*, *Proc. Natl. Acad. Sci. USA*, 97:3213-3218 (2000) (hereinafter "Colter"). The Examiner stated that Prockop, Prockop II and Furscht disclose cell populations isolated from human bone marrow which retain the capability to differentiate into various cell phenotypes including osteoblasts, chondrocytes and neuronal cell types which co-express CD49 and CD90 and do not express CD34 and CD45. The Examiner further stated that although Prockop and Prockop II are silent about the specific type of alpha integrin, in particular CD49c, Furscht discloses the expression of CD49c and Caplan is relied upon to show the inherent presence of CD49a, CD49b, CD49c and CD49e on mesenchymal stem cells derived from bone marrow. The Examiner also stated that Caplan teaches that the human mesenchymal stem cells derived from bone marrow express high levels of IL-6; Furscht describes mesenchymal stem cells derived from bone marrow that express additional markers including MCP1; Prockop II teaches isolated cell populations with doubling times less than 30 hours; and Colter demonstrates that cell populations of mesenchymal cells isolated from bone marrow have a doubling time of about 12 hours.

In addition, the Examiner stated that although the references relied upon for a rejection under 35 U.S.C. § 103(a) are silent or do not indicate growth rates of Applicants' claimed cell population, the same cell population of mesenchymal cells isolated from bone marrow which co-

express CD49 and CD90 are capable of growth rates as required by Applicants' pending claims. The Examiner also stated that Prockop, Prockop II and Furscht are silent regarding the amount of cells which co-express CD49 and CD90 and do not teach that isolated cell populations contain 91% of cells co-expressing CD49 and CD90. However, the Examiner stated that Furscht teaches positive and negative selection techniques known to those skilled in the art and that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply known techniques of cell sorting and enrichment to obtain an 91% pure cell population co-expressing CD90 and CD49 markers from the bone marrow mesenchymal stem cell populations with a reasonable expectation of success because the bone marrow mesenchymal stem cell populations contain cells expressing CD49 and CD90 markers and, thus, the bone marrow mix cell population is a reasonable source of the required cell product. The Examiner further stated that one of skill in the art would have been motivated to obtain a specific pure cell population co-expressing CD49 and CD90 for an expected benefit of collecting cell surface molecules and maximizing yields of collected amounts.

Prockop and Prockop II describe cell cultures of bone marrow stromal cells (MSC cells) that contain at least two different cell types, small and rapidly cell-renewing stem cells (RS cells) and large, more mature cells (mMSC cells). As noted by the Examiner, Prockop and Prockop II do not teach the expression of CD49c and a cell population that contains 91% of cells co-expressing CD49c and CD90.

Applicants' claimed invention, as set forth in pending Claims 14, 19-21, 23, 25 and 26 are directed to an isolated cell population derived from bone marrow, wherein greater than about 91% of the cells in the cell population co-express CD49c and CD90, and wherein the cell population has a doubling rate less than about 30 hours. The isolated cell population of the Applicants' claimed invention has the potential to differentiate into a pre-selected phenotype (Claim 19) selected from the group consisting of a chondrocyte, an astrocyte, an oligodendricyte, a neuron, an osteocyte, an osteoblast, an osteoclaste, a cardiomyocyte, a pancreatic islet cell, a skeletal muscle, a smooth muscle, a hepatocyte and a retinal ganglia cell (Claim 20). The isolate cell population can further include expression of p21, p53 (Claim 21), can be derived from human bone marrow (Claim 23), does not express CD34 and/or CD45 (Claim 25) and can further

express at least one trophic factor selected from the group consisting of BDNF, IL-6, NGF and MCP-1 (Claim 26).

As discussed above, the Examiner stated that the cell populations of Prockop and Prockop II do not disclose or suggest a cell population isolated from bone marrow wherein greater than about 91% of the cells of the cell populations co-express CD49c and CD90 and wherein the cell population has a doubling rate of less than about 30 hours.

The growth kinetics of the cell population illustrated in Figure 22 in Prockop II, referred to by the Examiner as depicting isolated cell populations with a doubling rate of about 30 hours, would require the presence of RS cells in a pool of marrow stem cells and could not occur in the presence of only mMSC cells in the absence of RS cells. As noted in page 13, lines 5-14, in reference to Figure 22, Prockop II states that mMSC cells replicate poorly, may arise from RS-2 cells, but could arise from RS-1 cells and that during cell growth, the cell population includes RS-1, RS-2 and mMSC cells. Further, as shown in Figure 26 and Table 3 of Prockop II, only mMSC cells are positive for CD90 and RS-1 cells are "dim" for CD90 and RS-2 cells are negative for CD90.

As described on pages 10, lines 15-16 and page 38, lines 29-32 in reference to Figure 8, Prockop II described Figure 8 as depicting the cell expansion achieved by low-density subculture. As shown in Figure 8, the percentage of colony forming units (CFU) varies depending upon the stage of cell expansion and harvesting of the cells.

As described on page 12, lines 23-29 of Prockop II, Figure 21 depicts the percentage of RS cells (RS-1 and RS-2) and the percentage of CFU in mesenchymal stem cells. According to Figure 21, a CFU of 39% (following the first plating and harvesting of cells as noted in Figure 8) would contain about 40-45% RS cells. Likewise, a CFU of 42% (as noted following the second plating and harvesting of cultures depicted in Figure 8) would contain, according to Figure 21, about 50% RS cells. Similarly, a CFU of 29% (as noted following the third plating and harvest of cultures depicted in Figure 8) would contain, according to Figure 21, about 35% RS cells. As discussed above, RS cells are either "dim" (RS-1 cells) or "negative" (RS-2 cells) for CD90 as noted on Table 3 of page 50 of Prockop II. Prockop teaches that only mMSC cells are positive for CD90 (see, for example, Table 3 on page 50 of Prockop II). Thus, the Examiner's reference to Figure 22 as depicting a population of cells with a doubling of less than about 30 hours, would

include a population of cells that contain between 29-42% CFU (according to Figure 8 which depicts cell expansion achieved by low-density subculturing) that includes between about 35-50% of the total RS cells (RS-1 and RS-2) shown in Figure 21. Thus, no greater than about 65% of the remaining cells could be mMSC cells, which are the cells Prockop and Prockop II teach as CD90 positive. Therefore, cells with population doubling times depicted in Figure 22 of Prockop II could not include a large population (e.g., greater than about 91% of the cell population) of large, mature mMSC cells, which are CD90 positive.

Furscht describes multipotent adult stem cells (MASC cells) including MASC cells derived from bone marrow aspirates. On page 24, lines 20-22, and as shown in Figure 2, Furscht describes a population of cells derived from bone marrow which have a doubling time of 36-48 hours for the initial 20-30 cell doublings followed by cell doubling time of 60-72 hours. On page 73, lines 10-18, Furscht describes a population of cells with a doubling time of 48-60 hours which stain positive with antibodies against several cell markers including CDw90.

Furscht does not remedy the deficiencies of Prockop or Prockop II. Specifically, there is no disclosure or suggestion in Prockop, Prockop II or Furscht, taken either separately or in any combination, of an isolated cell population derived from bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c and CD90 and wherein the cell population has a doubling rate of less than about 30 hours. Therefore, neither Prockop, Prockop II or Furscht, taken either separately or in any combination, disclose or suggest Applicants' claimed invention, as set forth in Claims 14, 19-21, 23, 25 and 26.

Caplan describes the isolation and purification of mesenchymal stem cells, including mesenchymal stem cells obtained from bone marrow. Caplan also describes the expansion of stem cells in culture without differentiation and monoclonal antibodies specific for human mesenchymal stem cells.

Caplan does not remedy the deficiencies of Prockop, Prockop II or Furscht. In particular, there is no disclosure or suggestion in Prockop, Prockop II, Furscht or Caplan, taken either separately or in any combination, of an isolated cell population derived from bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c andCD90 and wherein the cell population has a doubling rate less than about 30 hours. Therefore, Prockop, Prockop II, Furscht or Caplan, taken either separately or in any combination, do not

disclose or suggest Applicants' claimed invention, as set forth in Claims 14, 19-21, 23, 25 and 26.

Colter describes a subpopulation of cells derived from human mesenchymal stem cells that are small, proliferate rapidly and are precursors of more mature cells, which Colter refers to as recycling stem (RS cells). Darwin J. Prockop, of Prockop and Prockop II, is a co-author of Colter. As noted on page 3214, and as shown in Figure 2B, when Colter's cells are plated at low density, during the log phase of rapid growth the average doubling time is about 12 hours. On page 3215, and as shown in Figures 3 and 4, Colter states that the oldest progenitors in the cultures are RS-1 and RS-2 cells. Colter also states on page 3214:

> During the log phase of growth, the RS-2 cells decreased in number and the mMSCs rapidly expanded. During the late log phase, the RS-2 cells disappeared, and the RS-1 cells expanded.

Therefore, the population doubling times depicted in Figure 2B include a population of RS-1, RS-2 and mMSC cells which, according to Prockop II, discussed above, vary in CD90 expression. As discussed above, only the mMSCs cells of Prockop and Prockop II are positive for CD90; RS-1 cells are "dim" for CD90; and RS-2 cells are "negative" for CD90 (see, for example, page 50, Table 3 of Prockop II and paragraph 60, Table I, page 5 of Prockop). Therefore, Colter does not teach or suggest a cell population derived from bone marrow, wherein greater than 91% of the cells co-express CD49c and CD90 and wherein the cell population has a doubling rate of less than about 30 hours.

Colter does not remedy the deficiency of Prockop, Prockop II, Furscht or Caplan. Specifically, there is no disclosure or suggestion or Prockop, Prockop II, Furscht, Caplan or Colter, either taken separately or in any combination, of an isolated cell population having a doubling rate less than about 30 hours wherein greater than 91% of the cells of the isolated cell population co-express CD 49c and CD90. Therefore, Prockop, Prockop II, Furscht, Caplan or Colter, taken either separately or in any combination, disclose or suggest Applicants' claimed invention, as set forth in Claims 14, 19-21, 23, 25 and 26.

As stated in Section 2143.01, on page 2100-130 of the May 2004 edition of the Manual of Patent Examining Procedure (MPEP), prior art must suggest the desirability of the claimed

combination and the suggestion and motivation to modify the references must be found in the prior art.

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." [citations omitted]

Page 2100-131 of Section 2143.01 of the MPEP further states:

> The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.

(Emphasis in Original).

Neither, Prockop, Prockop II, Furscht, Caplan or Colter, taken separately or in any combination, as noted by the Examiner, teach or suggest an isolated cell population derived from bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c and CD90, and wherein the cell population has a doubling rate of less than about 30 hours, as set forth in Applicants' Claims 14, 19-21, 23, 25 and 26. Therefore, the Examiner has not established a *prima facie* case of obviousness since there is no suggestion or teaching, inherently or expressly, in Prockop, Prockop II, Furscht, Caplan or Colter, separately or in any combination, of Applicants' claimed cell population, as set forth in pending Claims 14, 19-21, 23, 25 and 26.

Applicants' claimed invention, as set forth in Claims 14, 19-21, 23, 25 and 26, meets requirements of 35 U.S.C. § 103(a) in view of Prockop, Prockop II, Furscht, Caplan or Colter.

Rejection of Claims 14, 19-21, 23, 25 and 26 Under 35 U.S.C. § 103(a)

Claims 14, 19-21, 23, 25 and 26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Prockop, Prockop II or Furscht in light of Caplan and Colter and further in view of van den Bos, C., *et al.*, *Cell Tissue Res.*, 293:463-470 (1998) (hereinafter "Bos") and Gartel, A.L., *et al.*, *Exp. Cell Res.*, 246:280-289 (1999) (hereinafter "Gartel").

The Examiner stated that although Prockop, Prockop II, Furscht, Caplan and Colter lack disclosure of the amount of p21 and p53 transcripts in cell populations of mesenchymal stem cells, Bos teaches that human mesenchymal stem cells derived from bone marrow express p21 and amounts related to particular culture conditions. The Examiner further stated that Gartel is relied upon to demonstrate the expression of p21 and p53 are related events in cell cycle progression. Furthermore, the Examiner stated that the bone marrow cell populations of Prockop, Prockop II and Furscht "might not be identical" to Applicants' claimed cell population with regard to the expression and amounts of p21 and p53 transcripts, and further stated:

> the differences between that are disclosed and that are claimed are considered to be so slight that the referenced cell populations are likely to possess the same characteristics of the claimed cell population particularly in view of the similar characteristics which they have been shown to share.

(Emphasis Added).

The Examiner concluded that, therefore, Applicants' claimed cell population would have been obvious to one of ordinary skill in the art.

The Examiner also stated that Applicants' claimed invention either does not require expression of p21 and p53 or the claim ranges are so broad as to encompass all types of cell culture and all types of cells. According to the Examiner, Applicants' claimed invention, as set forth in Claims 19 and 20, allows for any amount of p21 and p53.

As discussed above, Prockop, Prockop II, Furscht, Caplan and Colter, either taken separately or in any combination, do not teach or suggest Applicants' claimed invention.

Bos describes the programmed cell death, or apoptosis, of human mesenchymal stem cells upon seeding at low density and, with the onset of apoptosis, a decrease in the expression of the cyclin-dependent kinase inhibitors p21 and p27 in skeletal development.

As with Prockop, Prockop II, Furscht, Caplan and Colter, there is no disclosure or suggestion in Bos of the subject matter of Applicants' claimed cell population, which includes a cell population derived from bone marrow, wherein greater than 91% of the cells of the cell population co-express CD49c and CD90 and wherein the cell population has a doubling rate of less than about 30 hours. Therefore, Bos does not remedy the deficiencies of Prockop, Prockop II, Furscht, Caplan and Colter, since none of these references, taken either separately, or in any combination, disclose or suggest Applicants' claimed cell population.

Gartel reviews the literature regarding the transcriptional regulation of the p21 gene, including p53-dependent induction of p21 transcription and gene expression.

Gartel does not remedy the deficiencies of Prockop, Prockop II, Furscht, Caplan, Colter or Bos. Specifically, there is no disclosure or suggestion in Gartel of Applicants' claimed cell population. Gartel does not disclose or suggest an isolated cell population derived from bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c and CD90, wherein the cell population has a doubling rate of less than about 30 hours. Therefore, Gartel taken either separately or in any combination with Prockop, Prockop II, Furscht, Caplan, Colter or Bos, disclose or suggest Applicants' claimed invention.

Applicants' claimed invention, as set forth in Claims 14, 19-21, 23, 25 and 26 meet the requirement of 35 U.S.C. § 103(a) in view of Prockop, Prockop II, Furscht, Caplan, Colter, Bos or Gartel.

Response to Arguments

The Examiner stated that Applicants arguments filed in the Reply of December 22, 2003 distinguished Applicants' claimed invention from the references cited by the Examiner as cells cultured under low oxygen conditions. The Examiner stated that "low oxygen" culture conditions are not recited in the claims and that Applicants' cell population appears to be a cell population committed to nervous system cell lineage; yet, Applicants' claimed invention includes cells directed towards various lineages such as osteoclasts, muscle cells, pancreatic islets and

hepatocytes that would reasonably be expected to be produced under various and specific culture conditions.

In addition, the Examiner stated that Applicants' arguments failed to comply with 37 C.F.R. § 1.111(b) because:

> [T]hey [the arguments] amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

As discussed above, none of the references cited, either separately or in any combination, teach or suggest Applicants' claimed isolated cell population from bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c and CD90, and wherein the cell population has a doubling rate less than about 30 hours. Thus, none of the references cited by the Examiner, separately or in any combination, render the invention obvious. Therefore, Applicants' claimed invention, as set forth in pending Claims 14, 19-21, 23, 25 and 26, meets the requirements of 35 U.S.C. § 103(a).

With respect to the Examiner's statement that Applicants' arguments failed to comply with 37 C.F.R. § 1.111(b), Applicants note that arguments set forth in the December 23, 2002 Reply have resulted in withdrawal of rejections under 35 U.S.C. §§ 101, 112, second paragraph, 102(a)(b) and (e). In the Office Action, the Examiner states that rejections under 35 U.S.C. § 102(a), (b) and (e) have been withdrawn in light of Applicants' arguments. Therefore, the Examiner has reconsidered and undertaken further examination of the application in response to Applicants' arguments pointing out the specific distinctions believed to render the claims patentable over any references. As stated in 37 C.F.R. § 1.111(b):

> In order to be entitled to reconsideration or further examination, the applicant or patent owner must reply to the office action. . . . The reply must present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references. . . . The applicant's or patent owner's reply must appear throughout to be a *bona fide* attempt to advance the application or the reexamination proceeding to final action.

Therefore, contrary to the Examiner's assertion, the Reply filed on December 22, 2003 complies with 37 C.F.R. § 1.111(b).

SUMMARIES AND CONCLUSIONS

The subject matter of Claims 14, 19-21, 23, 25 and 26 meets the requirements of 35 U.S.C. § 103(a) in view of Prockop, Prockop II and Furscht in light of evidence by Caplan and Colter and in further view of Bos and Gartel. Therefore, Applicants respectfully request reconsideration and allowance of the claims under consideration.

If the Examiner feels a telephone conference would expedite prosecution of this application, she is invited to call Applicants' undersigned attorney.

Respectfully submitted,

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Dated: July 06, 2004